REMARKS

Claims 1, 6, 12-13, 26-27, 35-36, 44, 46, 52-53, 58, 60, and 74 are pending in the present application. Claims 1, 6, 27, 36, 46, 52-53, and 60 are amended to recite "DNA markers". Support for the amendments to claims 1, 6, 27, 36, 46, and 60 is found in the previously presented claims and in lines 11-21, p 14 of the specification. Support for the amendments to claims 52 and 53 is found in lines 18-19, page 4 of the specification. Claims 26, 35, 44, 58 and 74 are canceled without prejudice. Claims 97-102 are new claims. Support of the new claims is found in lines 1-19, p 33 of the specification. Reconsideration and allowance in view of the following amendments and remarks is requested.

Claim Objections

In the Office Action, claims 52 and 53 are objected to for reciting acronyms "RLM" and "ITM" respectively without providing the full terminology for the acronym.

In response to the objection claim 52 is amended to recite "RLM (regional lymph node metastasis)" and claim 53 is amended to recite "ITM (in-transit metastasis)".

Support for the amendments to claims 52 and 53 is found in lines 18-19, page 4 of the specification.

Rejections under 35 U.S.C. § 103(a)

In the Office Action, claims 1, 6, 12, 13, 26, 27, and 74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Soengas, et al. (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al. (US Patent 6156504).

Claim 1 is amended to recite a method of determining loss of heterozygosity of acellular DNA from a human subject, comprising "providing a sample containing acellular

DNA from a human subject, wherein the sample is selected from the group consisting of a blood sample, serum sample and plasma sample; and comparing one or more DNA markers on the acellular DNA with that on a control DNA for determination of loss of heterozygosity of the acellular DNA, wherein the DNA markers are selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346, and any combination thereof."

The Office Action asserted that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706 and D12S346 by use of peripheral blood, plasma, or serum as taught by Gocke, because Gocke teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. The ordinary artisan would further be motivated because, Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA. Thus as Gocke teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Gocke would have resulted in a method of detecting the presence of absence of D12S1657, D12S393, D12S1706 and D12S346 markers in [acellular] DNA from blood, serum, or plasma and from this detection allow the detection of melanoma." OA at p5-6. Applicants respectfully disagree.

The Office Action states "Soengas does not teach the use of [acellular] DNA from plasma, serum, or blood as a sample," OA at p5. Furthermore, Gocke recognized that "it has not been generally recognized that nucleic acid amplification assays can detect

tumor-associated extracellular mutated DNA, including oncogene DNA, in the plasma or serum fraction of blood. Furthermore, it has not been recognized that this can be accomplished in a clinically useful manner… It is known that small but significant amount of normal DNA circulate in the blood of healthy people… it had been generally presumed by those with skill in the art that circulating extracellular DNA either does not exist or would be of no clinical utility since it would be expected to be rapidly digested by plasma DNases…" (lines 6-26, col. 3)

Gocke provided a method of "preferential" amplification of the mutant DNA over the wildtype but not mutant extracellular DNA by selective digestion of the wildtype but not mutant DNA before and/or during and optionally after DNA amplification so that the mutant DNA is selectively amplified. ("Preferably, digestion of the extracted extracellular nucleic acid with an enzyme, … specifically cleaves wildtype but not mutant DNA in the portion of the sequence between the positions of the oligonucleotide primers used to amplify the DNA. Thus wildtype DNA in the sample cannot be amplified after restriction enzyme digestion, whereas mutant DNA can be amplified, and is preferentially amplified using the method of the invention… the amplification reaction is performed in the presence of a thermoresistant or thermostable restriction endonuclease, which endonuclease specifically cleaves wildtype (but not mutant) forms of extracellular tumor derived or tumor-associated nucleic acid species and therefore inhibits amplification of said species in the amplification…" (Lines 48-63, column 4.)

The present claim recites "comparing one or more DNA markers on the acellular DNA with that on a control DNA for determination of loss of heterozygosity of the acellular DNA." Gocke teaches away from determination of loss of heterozygosity by "comparing

one or more DNA markers on the acellular DNA with that on a control DNA" because Gocke teaches an ordinary artisan to amplify the mutant, not the wild type DNA. A sample containing acellular DNA that does not show loss of heterozygosity may show loss of heterozygosity if the sample undergoes the Gocke preferential amplification procedure because DNA that has loss of heterozygosity will be preferentially amplified over the DNA that has retained heterozygosity.

Thus, ordinary skill in the art at the time of the invention would not be motivated to combine Soengas in view of Gocke to compare DNA markers in a control DNA with that in acellular DNA from a blood sample, serum sample or plasma sample as claimed to determine loss of heterozygosity of the acellular DNA.

Similarly, claims 6 and 27 both recite "comparing one or more DNA markers on the acellular DNA with that on a control DNA for determination of loss of heterozygosity of the acellular DNA." Claims 12 and 13 depend from claim 6. Accordingly, claims 6, 12, 13, and 27 are patentable over Soengas in view of Gocke for at least the same reason set forth above with respect to claim 1.

Claims 26 and 74 are canceled without prejudice therefore the rejection is moot. Withdrawal of the rejections is thus respectfully requested.

In the Office Action, claims 35 and 58 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Soengas in view of Chapman et al (Journal of Clinical Oncology (1999) volume 17, pages 2745-2751), Healy (Oncogene (1998) volume 16, pages 2213-2218), and O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761).

Claims 35 and 58 are canceled without prejudice therefore the rejection is moot.

Withdrawal of the rejections is thus respectfully requested.

In the Office Action, claims 44 and 45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Soengas in view of Taback et al (Cancer Research (2001) volume 61, pages 5723-5726) and Chapman et al (Journal of Clinical Oncology (1999) volume 17, pages 2745-2751).

Claims 44 and 45 are canceled without prejudice therefore the rejection is moot. Withdrawal of the rejections is thus respectfully requested.

In the Office Action, claims 52 and 53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Soengas, Taback, and Chapman as applied to claim 44 and 45 above, and further in view of Yu (Cancer (1999) volume 86, pages 612-627).

Claims 52 and 53 are amended to depend from claim 46, which is not rejected to. Therefore withdrawal of the rejections is thus respectfully requested.

In the Office Action, claims 1, 6, 12, 13, 26, 27, and 74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Soengas in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571).

Claim 1 recites a method of detecting "DNA markers comprising providing a sample containing acellular DNA from a human subject, wherein-the sample is selected from the group consisting of a blood sample, serum sample and plasma sample; and

detecting one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346, and any combination thereof on the acellular DNA for analysis of loss of heterozygosity of the DNA markers."

The Office Action asserts that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of

detecting markers D12S1657, D12S393, D12S1706 and D12S346 by use of peripheral blood, plasma, or serum as taught by Fujiwara, because Fujiwara teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. The ordinary artisan would further be motivated because, Fujiwara teaches, '[t]he most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques.' Thus as Fujiwara teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Fujiwara would have resulted in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706 and D12S346 markers in [acellular] DNA from blood, serum, or plasma and from this detection allow the detection of melanoma." OA at 22-23. Applicants respectfully disagree.

The Office Action states "Soengas does not teach the use of [acellular] DNA from plasma, serum, or blood as a sample," OA at p5. Fujiwara showed that the presence of microsatellite markers of DNA markers is not necessarily identical or consistent in tumor cells and as acellular DNA (Table 2, patients 1, 3, 6, 8-10, 14-17, 19-20, 23 and 30-31, p 1569). As pointed out in the present specification, the location of the APAF-1 gene in acellular DNA is between D12S1657-D12S346 (line 27, p 28 – line 6, p 29), which is different from Soengas. Although the location of the APAF-1 gene is not within the scope of the present claim, the different location on acellular DNA and tumor cellular DNA

shows that one skilled in the art will not have a reasonable expectation that the DNA markers are the same for acellular DNA and DNA in tumor cells. Fujiwara does not teach the DNA markers D12S1657, D12S393, D12S1706, and D12S346 associated with APAF-1 gene of DNA in tumor cells will be the same DNA markers for APAF-1 gene of acellular DNA. Therefore, Fujiwara does not cure the deficiency of Soengas.

Similarly, claims 6 and 27 both recites analysis of the DNA markers D12S1657, D12S393, D12S1706, and D12S346 in acellular DNA in a blood sample, serum sample or plasma sample. Claims 12 and 13 depend from claim 6. Accordingly, claims 6, 12, 13, and 27 are patentable over Soengas in view of Fujiwara for at least the same reason set forth above with respect to claim 1.

Claims 26 and 74 are canceled without prejudice therefore the rejection is moot. Withdrawal of the rejections is thus respectfully requested.

In the Office Action, claims 35-36, 58 and 60 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Soengas in view of Fujiwara as applied to claims 1, 6, 12, 13, 26, 27, and 74 above, and further in view of Chapman, Healy, and O'Day.

Claims 35 and 58 are canceled without prejudice therefore the rejection is moot. Withdrawal of the rejections is thus respectfully requested.

Claims 36 and 60 recites DNA markers D12S1657, D12S393, D12S1706, and D12S346 in acellular DNA in a blood sample, serum sample or plasma sample. Chapman, Healy and O'Day, alone or together, do not cure the deficiency of Soengas and Fujiwara. Accordingly, claims 36 and 60 are patentable over Soengas in view of Fujiwara, and further in view of Chapman, Healy, and O'Day, for at least the same reason set forth above with respect to claim 1.

New claim 97 depends from claim 1 and recites "DNA markers that have lost heterozygosity and the DNA markers that have retained heterozygosity are both amplified." Support of the new claim is found in lines 1-19, p 33 of the specification because according to the procedure of the specification, the DNA markers are amplified regardless of whether the DNA markers have lost heterozygosity or retained heterozygosity. Therefore no new matter is introduced in claim97. Because claim 1 is patentable as set forth above, claim 97 is patentable for at least the same reason as set forth above with regard to claim 1.

Similarly, new claim 98 depends from claim 6, new claim 99 depends from claim 27, new claim 100 depends from claim 36, new claim 101 depends from claim 46 and new claim 102 depends from claim 60. The new claims 98-102 also recite recites "DNA markers that have lost heterozygosity and the DNA markers that have retained heterozygosity are both amplified," which is supported by the specification for the reason set forth above with regard to claim 97. Therefore no new matter is introduced in claims 98-102 and they are patentable for at least the same reason as set forth above with regard to their respective independent claims 6, 27, 36, 46 and 60.

CONCLUSION

In view of the foregoing, it is submitted that the claims are in condition for allowance. A Notice of Allowance is requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to contact the undersigned at 310-788-9900.

Respectfully submitted,

Perkins Coie LLP

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/Michael J. Wise/
Michael J. Wise
Registration No. 34,047

Correspondence Address:
Customer No. 34055
Perkins Coie LLP
P.O. Box 1247
Seattle, Washington 98111-1247
(310) 788-9900